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10/559,375	02/02/2007	Peter F. Muhlradt	03100262AA	3623

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EXAMINER	
JUEDES, AMY E	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,375	MUHLRADT ET AL.	
	Examiner	Art Unit	
	AMY E. JUEDES	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10 and 25-38* is/are pending in the application.

4a) Of the above claim(s) *34-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10 and 25-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 3/9/09, is acknowledged.
Claims 1-9 and 11-24 have been cancelled.
Claim 10 has been amended.
Claims 25-38 have been added.
Claims 10 and 25-38 are pending.

2. Applicant's election with traverse of group II, claims 10 and 25-33, drawn to a therapeutical composition comprising dendritic cells, in the reply filed on 3/9/09, is acknowledged.

Applicant's traversal is on the grounds that it would not be an undue burden to examine the product of group IV along with the dendritic cell compositions of group II, since the product of group IV is used for making the dendritic cells of group II. This is not found to be persuasive because the products of groups II and IV (i.e. a dendritic cells and a composition comprising a lipopeptide and cytokine receptor agonist) are recognized divergent subject matter and classified in different classes. In addition, the different products are distinct because their structures are different and are therefore capable of separate manufacture, use and sale. Furthermore, although the dendritic cells of group II are produced using the lipopeptide/agonist of group IV, a search for the dendritic cells of group II is not limited to those made using said lipopeptide/agonist, since the dendritic cells might have been produced using another method. Furthermore, the product of group IV is drawn to a pharmaceutical composition comprising a lipopeptide/agonist, which would not necessarily be required for an in vitro method of dendritic cell production. Additionally, a search for the product of group IV would require a more extensive search than that for group II, since the composition comprising a lipopeptide/agonist might have been used for a different purpose than the method of producing dendritic cells of group II. Therefore these products are distinct, and searches for both would place an undue burden upon the examiner due to divergent subject matter of each Group. Further, a prior art search also requires a

literature search. It is an undue burden for the examiner to search more than one invention.

The requirement is still deemed proper and is therefore made FINAL.

Claims 34-38 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 10 and 25-33 read on the elected invention and are under examination.

3. Claim 10 is objected to for the following informalities: The claim recites a composition of dendritic cells, "said DC have" acquired the property to drive a T helper 1 response. It would be more grammatically correct if the claim were amended to read a composition of dendritic cells, "wherein said DC" have acquired said property. Additionally, claim 10 recites that the DC are cultured in the present of "at least" TLR2 and TLR6 agonist. The claim would be more grammatically correct if it were amended to read that the DC are culture in the presence "of at least one" TLR2 and TLR6 agonist.

4. Claim 25 is objected to for the following informalities: "*Mycoplasma fermentans*" should be italicized.

5. Claim 32 is objected to for the following informalities: The claim recites "cuculturing". The claim should be amended to recite "coculturing". Additionally, it is assumed that the recitation of "allergenic" is a typographical error, and the claim was intended to recited "allogenic".

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

A) Claim 29 recites the broad recitation "progenitor derived DC" and "in vivo existent DC", and the claim also recites "monocyte derived DC" and "blood derived DC", which is the narrower statement of the range/limitations, respectively.

B). Claim 32 recites the broad recitation "at least 24 hours", and the claim also recites "at least 3 days" which is the narrower statement of the range/limitations. Claim 32 also recites a limitation of a time period of "up to several days", which would also include time ranges the are outside of the other recited ranges (i.e. time frames less than 24 hours or 3 days). Thus, the metes and bounds of the recited timeframes encompassed by the claims cannot be determined.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10 and 25-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention. Specifically, there is insufficient written description to demonstrate that applicant was in possession of the claimed genus of "IFN-gamma receptor agonists" or "IFN-gamma variants".

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

The instant claims are drawn to a method employing a genus of "IFN-gamma receptor agonists". This might encompass a broad range of structurally different agonists including small molecules, antibodies, peptides, proteins, etc. The specification does not disclose a correlation between the structure of the agonists and the function of stimulating IFN-gamma receptor. Furthermore, there is no art recognized correlation between structure and function for the agonists as broadly claimed. Additionally, even when the claims are limited to "variants" of IFN-gamma, this still might encompass a broad range of different polypeptides or peptides. The specification does not disclose a correlation between the structure of IFN-gamma variants, and their ability to act as agonists for the INF-gamma receptor. Likewise, there is no art recognized correlation between said structure and function. Furthermore, the instant specification only discloses a single species of IFN-gamma receptor agonist (IFN-gamma) and does not disclose any IFN-gamma "variants". This is not representative of the broad range of structurally different "agonists" or "variants" encompassed by the instant claims. Thus, one of skill in the art would conclude that the specification fails to provide adequate written description to demonstrate that Applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F. 3d 1559, 43, USPQ2d

1398.

8. Claim 32 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a therapeutical composition comprising dendritic cells adapted as a vaccine for the treatment of malignancies, allergic disorders, and infectious disorders including viral, bacterial, and fungal infections,

does not reasonably provide enablement for:

a therapeutical composition comprising dendritic cells adapted as a vaccine for the treatment of parasitic infections, autoimmune disorders, and host-versus graft or graft versus host reactions.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, *in re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

"The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)" The MPEP further states that physiological activity can be considered inherently unpredictable.

The specification provides insufficient guidance to use the therapeutical compositions as broadly claimed. The instant claim is drawn to a therapeutical composition comprising dendritic cells that drive Th1 immune responses. Dendritic cells that induce Th1 T cells are well known to be useful for treating cancer or certain types of infections. However, the instant claims encompass using the dendritic cell compositions for treating other diseases, including autoimmune diseases, graft vs. host or host vs. graft disease, and parasitic infections. However, Th1 cytokines are pathogenic in autoimmune disease (see Diveu et al., 2008). Likewise, Th1 cytokines contribute to graft rejection (see Lakkis, 1998). Furthermore, a Th2 response is critical in controlling parasitic infections, and deviation to a Th1 response can be detrimental in the control of said infections (see Pearce et al., 2004). Therefore, using a dendritic cell that stimulates a Th1 immune response to treat autoimmune disease, graft rejection or GVHD, and parasitic infections is highly unpredictable. Thus, based on the unpredictability of the art, the instant specification must provide a sufficient and enabling disclosure commensurate in scope with the instant claim. The specification demonstrates that the dendritic cells of the claims induce a Th1 immune response, and provides examples that reagents that induce said Th1 skewing dendritic cells are useful for treating allergy. No examples are provided relating to autoimmune disease, graft rejection/GVHD, or parasitic infection. Thus, based on the lack of guidance provided by the instant specification, and the unpredictability of the art, it would require undue experimentation to use the therapeutical compositions as broadly claimed.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 10 and 25-33 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over WO 03/022215, as evidenced by Farhat et al., 2008, and Heldewein et al., 2003.

WO 03/022215 teaches compositions comprising dendritic cells that are obtained by culturing said dendritic cells in the presence of BCG and IFN-gamma (see page 4 in particular). WO 03/022215 also teaches compositions comprising said dendritic cells co-cultivated with autologous T lymphocytes, including for 24 hours (see pages 6, 17, and 23, in particular). WO 03/022215 also teaches loading said dendritic cells with antigen (see page 4, in particular). WO 03/022215 also teaches that the dendritic cells are suitable for inducing a Th1 response (see page 6, in particular). WO 03/022215 also teaches that the dendritic cell compositions can be administered to a subject in need of immunostimulation (i.e. as a therapeutic composition, see page 17-18 in particular). WO 03/022215 also teaches monocyte derived dendritic cells (see page 5 in particular). WO 03/022215 teaches using the dendritic cells for injection into a tumor (i.e. dendritic cell composition "adaptable as a vaccine for the treatment of malignancies", see page 18, in particular). WO 03/022215 also teaches washing the dendritic cells extensively and resuspending the cells in X-VIVO medium (i.e. a physiological medium, see page 23 in particular). Furthermore, as evidenced by Heldewein et al., BCG is a TLR2 agonist (see page 284, in particular). Additionally, as evidenced by Farhat et al., ligands that signal through TLR2 or TLR2/TLR6 heterodimers (i.e. TLR2 and TLR6 agonists) induce an identical signaling pathway and gene expression profile (see page 693, in particular). The instant claims are drawn to a product, a dendritic cell, and the patentability of a product does not depend on its method of production (see MPEP 2113). Therefore, the product by process limitations of the instant claims wherein the dendritic cells are produced using a particular TLR2/TLR6 agonist does not distinguish the dendritic cells from those of WO

03/022215, since all TLR2 or TLR2/6 agonists would induce identical signaling pathways and gene expression profiles (i.e. would result in dendritic cells with identical properties). Thus, even though the dendritic cells of WO 03/022215 have been produced by a method different than that of the instant claims (i.e. culture with IFN-gamma and a TLR2 agonist, instead of IFN-gamma and a TLR2/TLR6 agonist such as MALP-2), they are structurally identical to the TH1 inducing dendritic cells of the instant claims.

Thus, the reference clearly anticipates the invention.

11. Claims 10, 25-29, and 33 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Re et al., 2001 (of record).

Re et al. teach a composition comprising dendritic cells that are obtained by culturing said dendritic cells in the presence of peptidoglycan (PGN) and IFN-gamma (see page 37698 and Fig. 5, in particular). Re et al. also teach that PGN is an agonist of TLR2 and TLR6 (see page 37696, in particular). Re et al. teach that the dendritic cells produce IL-12, which induces TH1 polarization (see page 37698 and Fig. 5, in particular). Re et al. teach monocyte derived dendritic cells (see page 37693, in particular). Furthermore, the TLR2/TLR6 agonist of Re et al. can be considered a "derivative" of bisacyloxypropyl-S-cystein or of MALP-2, since it stimulates the same TLR receptors. Furthermore, even if the TLR2/TLR6 ligand of Re et al. is different than those of the instant claims (for example, those recited in claim 27), the instant claims are drawn to a product, and the patentability of a product does not depend on its method of production. The PGN taught by Re et al. stimulates the exact TLR receptors recited in the instant claims, and would thus result in a dendritic cell with identical properties irrespective of the particular TRL2/TLR6 agonist used. Furthermore, regarding the limitation of a "therapeutical composition", it is noted that this refers to an intended use of the dendritic cell compositions and does not carry patentable weight in the absence of a structural different in the product. Re et al. disclose a composition comprising TLR2/TLR6 agonist and IFN-gamma receptor matured dendritic cells in RPMI 1640 medium (see page 37695 in particular). Tissue culture medium is

compatible with physiologic conditions, and not incompatible with a therapeutic use. Additionally, the instant specification on pages 4-5 discloses that agonists added to a culture of dendritic cells can be used as a therapeutic composition as such. Re et al. disclose said agonists added to a culture of dendritic cells. Thus, based in the teachings of the instant specification, the cell compositions taught by Re et al. are structurally identical to the "therapeutic" composition of the instant claims.

Thus, the reference clearly anticipates the invention.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes whose telephone number is 571-272-4471. The examiner can normally be reached on 7am to 3:30pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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